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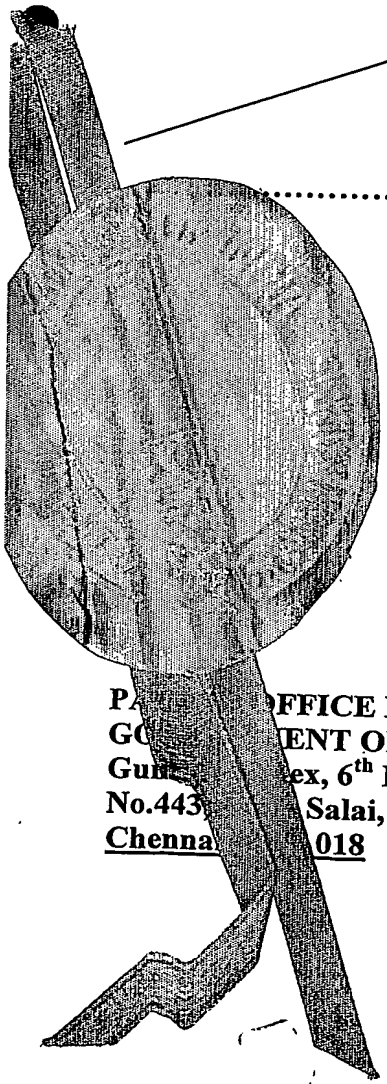
PCT/IN03/00389

IN03/00389

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Provisional Specification of the extract of Patent Application No. 925/MAS/2002 dated 12/12/2002 by M/s. JAWAHARLAL NEHRU CENTRE FOR ADVANCED SCIENTIFIC RESEARH, Jakkur Post, Bangalore – 560 064, Karnataka, INDIA.

.....



.....In witness thereof

I have hereunto set my hand

Dated this the 16th day of January 2004
26th day of Pausa 1925 (Saka)

M.S. Venkataraman

(M.S. VENKATARAMAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

P[illegible]FFICE BRANCH
G[illegible]ENT OF INDIA
Gu[illegible]ex, 6th Floor, Annex.II
No.443[illegible] Salai, Teynampet,
Chenna[illegible]018

FORM 1
THE PATENTS ACT 1970
(39 OF 1970)

APPLICATION FOR GRANT OF PATENT

(see sections 5(2), 7, 54 and 135 and rule 33 a)

We, Administrative Officer, Jawaharlal Nehru Centre for Advanced Scientific Research, Jakkur Post, Bangalore-560 064, hereby declare:

a) that we are in possession of an invention titled **Modulators (activators/inhibitors) of histone acetyltransferases.**

b) that the provisional / complete specification relating to this invention is filed with this application

c) that there is no lawful ground of objection to the grant of a patent to us,

Further declare that the inventor for the said invention are **Shri Karanam Balasubramanyam**, at 145, Padmalaya, 2nd H Main, 11th Block, II Stage, Nagarabhavi, Bangalore-72, an Indian national, **Shri Venkatesh Swaminathan** at 'SANSKAR' Flat No. 1A, 8 Lake Range, Kolkata-26, an Indian national and **Dr. Tapas Kumar Kundu**, residing at No.JJ-D1 Type Quarters, Jawaharlal Nehru Centre for Advanced Scientific Research, Jakkur Campus, Jakkur Post, Bangalore-64, an Indian National.

We claim the priority from the application(s) filed in convention countries particulars of which are as follows:

a. Not applicable
b. Not applicable
c. Not applicable
d. Not applicable
e. Not applicable

We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant/patentee:

a. Not applicable
b. Not applicable

We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on date **not applicable** under section 16 of the Act.

a. Not applicable
b. Not applicable

That we are the assignee or legal representative of the true and first inventors.

Cont'd.....2

That our address for service in India is as follows:

Dr. H.M. Jagannatha
Flat No.1, Chitrakoot Annexe,
55/1-A, 4th Main, 18th Cross, Malleswaram,
Bangalore-560 055.
Tel: 331 2542
E-mail: jagannatha@~~inablers.com~~ vsnl.net

Following declaration was given by the inventor(s) or applicant(s) in the convention country:

We the true and first inventors for this invention or the applicant(s) in the convention country declare that the applicant(s) herein are our assignee or legal representative. KARANAM BALASUBRAMANYAM - K Balasubramanyam, VENKATESH SWAMINATHAN - Swaminathan, TAPAS KUMAR KUNDU - Tapas Kumar Kundu.

That to the best of our knowledge, information and belief that fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

The following are the attachment with the application:

a) ~~Complete~~/Provisional specification (in triplicate)
b) ~~Drawings~~
c) ~~Priority document~~(s)
d) Statement and Undertaking on Form-3
e) Power of Authority

Fee of Rs.5,000/- (Rupees Five Thousand Only) vide Cheque No. 180257A dated 09/12/02 drawn on CORPORATION BANK Malleswaram 18th Cross Bangalore enclosed

We request that a patent may be granted to us for the said invention

Dated this 9th December 2002

(A.N.Jayanchandra)
Administrative Officer
Jawaharlal Nehru Centre for
Advanced Scientific Research
Jakkur Post, Bangalore-64.

To:

The Controller of Patents,
The Patent Office,
CHENNAI

FORM 2

THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION :
(see Section 10)

Modulators (activators/inhibitors) of histone acetyltransferases.

We, **JAWAHARLAL NEHRY CENTRE FOR ADVANCED SCIENTIFIC RESEARCH, JAKKUR, BANGALORE 560 064, INDIA**

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed :

Field of invention

This invention relates to the field of novel anticancer agents for therapeutic application in human medicine.

Abstract :

In this patent we describe the design and synthesis of the amide derivatives anacardic acid as activator molecules of Histone acetyltransferases p300. We have also found that anacardic acid is a potent HAT inhibitor of p300 (IC_{50}~15μM) and pCAF (IC_{50}~5μM). The activator molecule significantly enhances the p300 HAT dependent transcriptional activation from *in vitro* assembled chromatin template without effecting the *in vitro* DNA transcription. It also doesn't affect histone deacetylase activity. These compounds should be useful as biological switching molecules for evaluating the role of p300 and other HATs in cellular functions and may be useful as new chemical entities for the development of anticancer drugs.

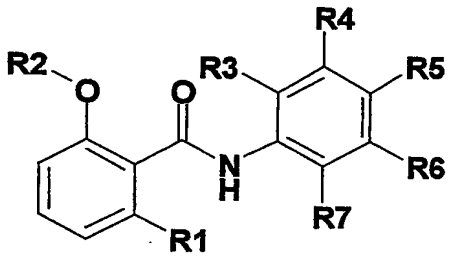
Prior art

Eukaryotic DNA is organized as a highly complex nucleo-protein chromatin structure, the unit of which is nucleosome. There are two copies of four different histones, H3, H2B, H2A, and H4, which is wrapped around by 146 base pairs of DNA in the nucleosome. Therefore, for any process that requires access to the DNA (e.g. transcription, replication, recombination and repair), the chromatin needs to be opened by the remodeling systems. Two different biochemical processes modify chromatin structure, which are the covalent modifications of histones tails and the ATP dependent chromatin remodeling. Among the several covalent modifications of histones, the reversible acetylation of lysine residues in histones, holds a prominent position in transcriptional regulation. Acetylation of histones is a diagnostic feature for the transcriptionally active genes, whereas deacetylation indicates the repressed state of the gene. A balance between the acetylation and deacetylation of histones regulates transcription. Dysfunction of the enzymes involved in these events, the histone acetyltransferases (HATs) and histone deacetylases (HDACs) is often associated with several diseases predominantly manifestation of cancer. These enzymes thus become potential new targets for antineoplastic therapy.

NATURE OF INVENTION

In this patent we describe the design and synthesis of the amide derivatives anacardic acid as activator molecules of Histone acetyltransferases p300. We have also found that anacardic acid is a potent HAT inhibitor of p300 (IC_{50}~15μM) and pCAF (IC_{50}~5μM). The activator molecule significantly enhances the p300 HAT dependent transcriptional activation from *in vitro* assembled chromatin template without effecting the *in vitro* DNA transcription. It also doesn't affect histone deacetylase activity. These compounds should be useful as biological switching molecules for evaluating the role of p300 and other HATs in cellular functions and may be useful as new chemical entities for the development of anticancer drugs. The compounds of interest in this invention are described below :

1. A compound of structural formula for activator of Histone acetyltransferases:



Wherein

R1 may be H, Methyl, Ethyl, n-Propyl , Isopropyl, n-butyl, t-butyl, C_8H_{18} ,$C_{15}H_{26}$, $C_{15}H_{28}$, $C_{15}H_{30}$, $C_{15}H_{32}$.

R2 may be H, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl and *t*-butyl

R3 may be H, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl and *t*-butyl, CF_3, CCl_3, CI_3, F, Cl, I, NO_2, CN

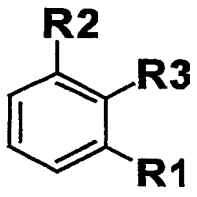
R4 may be H, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl and *t*-butyl, CF_3, CCl_3, CI_3, F, Cl, I, NO_2, CN

R5 may be H, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl and *t*-butyl, CF_3, CCl_3, CI_3, F, Cl, I, NO_2, CN

R6 may be H, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl and *t*-butyl, CF_3, CCl_3, CI_3, F, Cl, I, NO_2, CN

R7 may be H, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl and *t*-butyl, CF_3, CCl_3, CI_3, F, Cl, I, NO_2, CN

2. A compound of structural formula for inhibitor of Histone acetyltransferases:



Wherein

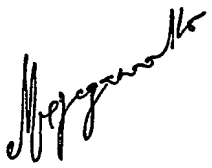
R1 may be H, Methyl, Ethyl, n-Propyl , Isopropyl, n-butyl, t-butyl, C_8H_{18} ,$C_{15}H_{26}$, $C_{15}H_{28}$, $C_{15}H_{30}$, $C_{15}H_{32}$.

R2 may be H, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl and *t*-butyl

R3 may be COOH.

These compounds should be useful as biological switching molecules for evaluating the role of p300 and other HATs in cellular functions and may be useful as new chemical entities for the development of anticancer drugs.

Dated this 9th Day of December 2002



H.M. Jagannatha
Agent for the applicant

To,
The Controller of Patents,
The Patent Office,
Chennai